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August 22, 2005

Christine A. Goddard, Ph.D.
Registered Patent Agent
Direct Phone 215.665.2191
cagoddard@cozen.com

VIA FACSIMILE 011 49 89 2399
4465/FEDERAL EXPRESS

The European Patent Office (EPO)
Directorate General 2
D-80298 Munich
Germany

Re: Amendment Under Article 34 of the PCT
International Application No. PCT/US2004/019279 filed 16 June 2004
Arena Pharmaceuticals, Inc.
Reference No. 64.WO1

Dear Sirs:

Applicant wishes the international preliminary examination to start on the basis of the description as originally filed and the claims as amended according to the attached Amendment under Article 34 of the Patent Cooperation Treaty. Demand for international preliminary examination was previously requested on 15 April 2005. This amendment is timely filed within 3 months of the mailing date (24 May 2005) of the International Search Report and Written Opinion of the International Searching Authority.

The claims have been amended as indicated below.

Claims 1-357, 359, 361, 363, 366-389, 394, 396, 397, 399-424, 427, 429-453, 456, 458, 460, 465-491, 494, 498-521, 524, 530-563, 567-590, 596-619, 624-635, 640-649 have been canceled.

Claims 390, 425, 454, 492, 522, 564, 591, 620, 636, and 650 have been amended to eliminate reference to variables R^{7a} and R^{7b} which do not appear in the chemical formulas of the claims.

Claims 365, 462, 497, 528, and 566 have been amended to replace "Br" with "Cl" for the variable X^2. Support for this amendment can be found in the description on page 37, line 26.

Claim 395 has been amended to include the subject matter of claim 394 (canceled).

Claim 595 has been amended to replace "Formula Va" with "Formula Vb." Support for the amendment can be found in the description on page 42, lines 10-11.

New Claims 12, 31, 36, 50, 55 and 57 (of the newly renumbered claim set provided herein) have been added. Support can be found, for example, on page 37, line 22; page 37, line 27; page 37, lines 29-30; page 42, lines 10-11; and page 43, lines 13-14 of the specification.

The proposed amendments do not add new matter or go beyond the subject matter of the application as-filed.

In view of the above-mentioned amendments, the claims have been renumbered. A table correlating original claim number with new claim number is attached.

Replacement sheets for pages 61-78 of the application are enclosed. Please note that because of claim cancellation, the remaining pages 79-143 are deleted from the application and the Abstract is now located on page 78 instead of page 143.

If you have any questions, please do not hesitate to contact me.

Sincerely,

COZEN O'CONNOR

By: Christine A. Goddard, Ph.D.
CAG/jsj
Enclosures

Table showing claim renumbering scheme

Original Claims No.	New Claim No.
358	22
360	23
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Original Claims No.	New Claim No.
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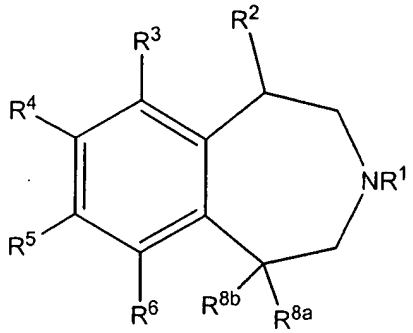
What is claimed is:

1. A process for preparing a compound of Formula V:



V

or salt thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

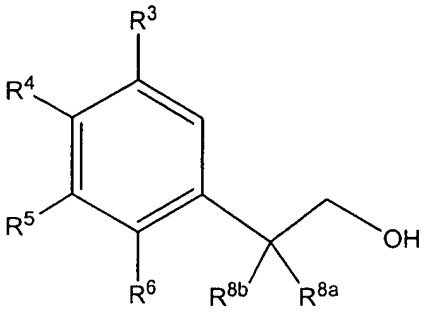
R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

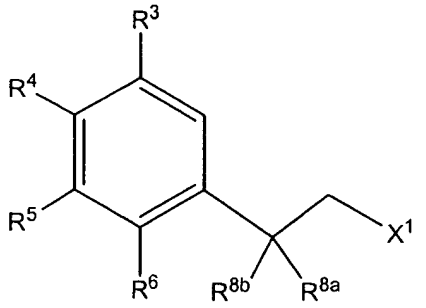
comprising:

a) reacting a compound of Formula XII:



XII

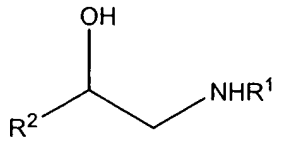
with a halogenating/sulfonating reagent for a time and under conditions suitable for forming a compound of Formula XI:



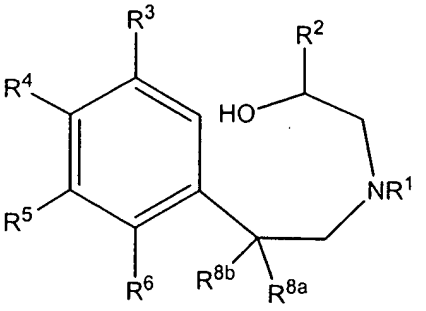
XI

wherein X^1 is a leaving group;

b) reacting said compound of Formula XI with a compound of Formula:



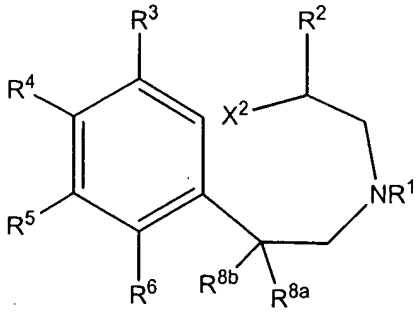
or salt thereof, for a time and under conditions suitable for forming a compound of Formula X:



X

or salt thereof;

c) reacting said compound of Formula X with a further halogenating/sulfonating reagent for a time and under conditions suitable for forming a compound of Formula IX:



IX

or salt thereof;

wherein X^2 is halo or SO_2R" and R" is C_1-C_8 alkyl, aryl, or heteroaryl each optionally substituted by one or more halo, cyano, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy; and

d) reacting said compound of Formula IX with a cyclizing reagent for a time and under conditions suitable for forming said compound of Formula V.

2. The process of claim 1 wherein said cyclizing reagent is $AlCl_3$.

3. The process of claim 1 wherein said halogenating/sulfonating reagent is PBr_3 or PCl_3.

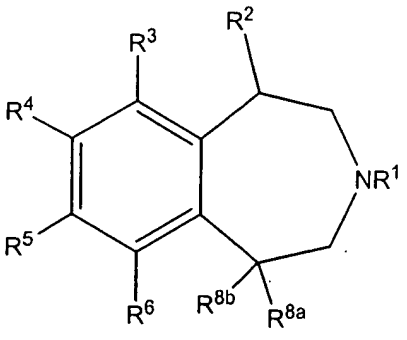
4. The process of claim 1 wherein said further halogenating/sulfonating reagent is $SOBr_2$ or $SOCl_2$.

5. The process of claim 1 wherein X^2 is Cl.

6. The process of claim 1 wherein X^1 is Br.

7. The process of claim 1, 5, or 6 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

8. A process for preparing a compound of Formula V:



V

or salt thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

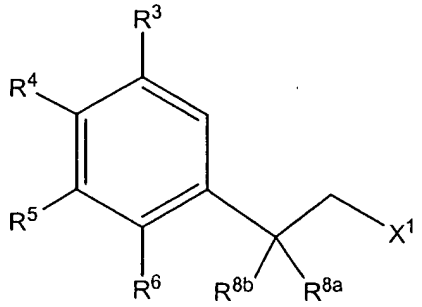
R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

comprising:

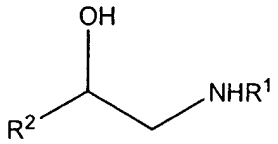
a) reacting a compound of Formula XI:



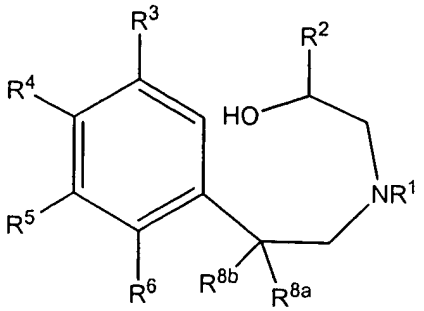
XI

wherein X^1 is a leaving group,

with a compound of Formula:



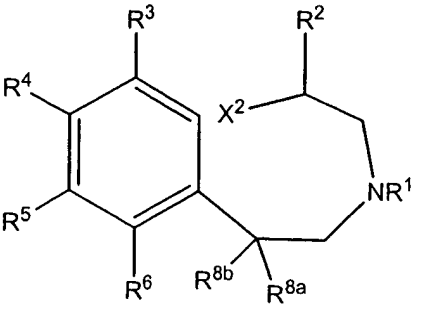
or salt thereof, for a time and under conditions suitable for forming a compound of Formula X:



X

or salt thereof;

b) reacting said compound of Formula X with a halogenating/sulfonating reagent for a time and under conditions suitable for forming a compound of Formula IX:



IX

or salt thereof;

wherein X^2 is halo or SO_2R" and R" is C_1-C_8 alkyl, aryl, or heteroaryl each optionally substituted by one or more halo, cyano, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy; and

c) reacting said compound of Formula IX with a cyclizing reagent for a time and under conditions suitable for forming said compound of Formula V.

9. The process of claim 8 wherein said cyclizing reagent is $AlCl_3$.

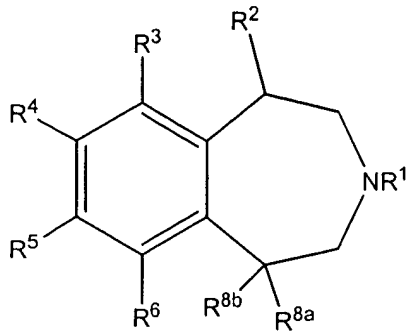
10. The process of claim 8 wherein said halogenating/sulfonating reagent is $SOBr_2$ or $SOCl_2$.

11. The process of claim 8 wherein X^2 is Cl.

12. The process of claim 8 wherein X^1 is Br.

13. The process of claim 8, 11, or 12 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

14. A process for preparing a compound of Formula V:



V

or salt thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

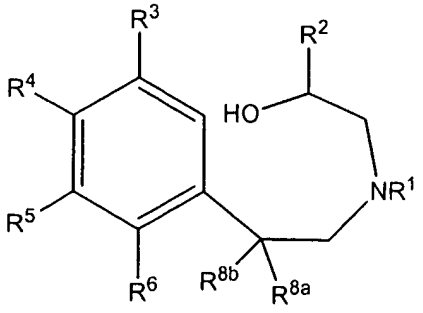
R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

comprising:

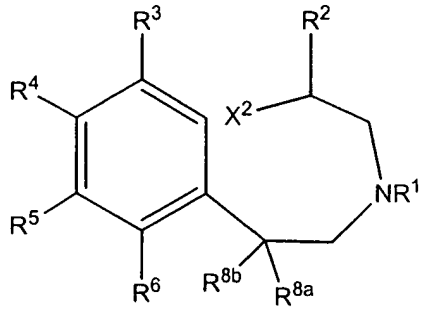
a) reacting a compound of Formula X:



X

or salt thereof;

with a halogenating/sulfonating reagent for a time and under conditions suitable for forming a compound of Formula IX:



IX

or salt thereof;

wherein X^2 is halo or SO_2R" and R" is C_1-C_8 alkyl, aryl, or heteroaryl each optionally substituted by one or more halo, cyano, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy; and

b) reacting said compound of Formula IX with a cyclizing reagent for a time and under conditions suitable for forming said compound of Formula V.

15. The process of claim 14 wherein said cyclizing reagent is $AlCl_3$.

16. The process of claim 14 wherein said reacting of step (b) is carried out in the presence of 1,2-dichlorobenzene.

17. The process of claim 14 wherein said halogenating/sulfonating reagent is $SOBr_2$ or $SOCl_2$.

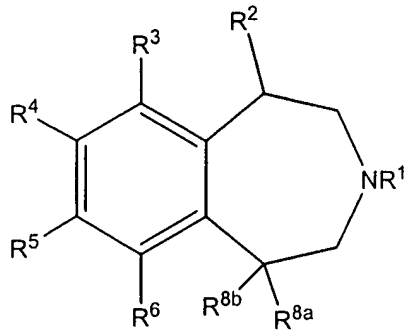
18. The process of claim 14 wherein X^2 is Cl.

19. The process of claim 14 wherein said reacting of step (a) is carried out in the presence of solvent.

20. The process of claim 19 wherein said solvent comprises dimethylformamide or toluene.

21. The process of claim 14 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

22. A process for preparing a compound of Formula V:



V

or salt thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

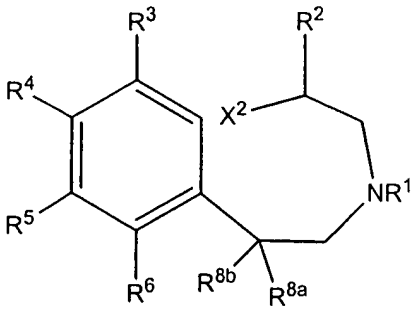
R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

comprising reacting a compound of Formula IX:



IX

or salt thereof, wherein X^2 is halo or SO_2R" and R" is C_1-C_8 alkyl, aryl, or heteroaryl each optionally substituted by one or more halo, cyano, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy, with a cyclizing reagent for a time and under conditions suitable for forming said compound of Formula V.

23. The process of claim 22 wherein said cyclizing reagent is $AlCl_3$.

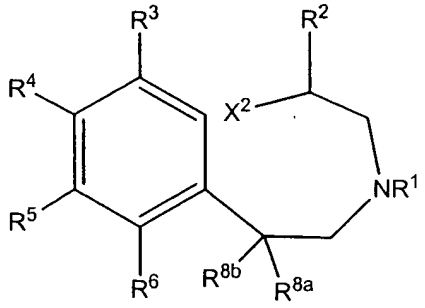
24. The process of claim 22 wherein said reacting is carried out in the presence of 1,2-dichlorobenzene.

25. The process of claim 22 wherein said reacting is carried out at a temperature between about 100 and about 150 °C.

26. The process of claim 22 wherein X^2 is Cl.

27. The process of claim 22 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

28. A process for preparing a compound of Formula IX:



IX

or salt thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo,

C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

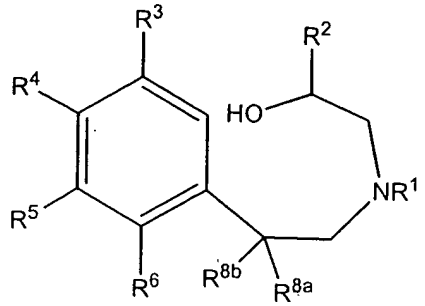
R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl;

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring; and

X^2 is halo or SO_2R"; and

R" is C_1-C_8 alkyl, aryl, or heteroaryl each optionally substituted by one or more halo, cyano, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy;
comprising reacting a compound of Formula X:



X

or salt thereof, with a halogenating/sulfonating reagent for a time and under conditions suitable for forming said compound of Formula XI.

29. The process of claim 28 wherein said halogenating/sulfonating reagent is $SOBr_2$ or $SOCl_2$.

30. The process of claim 28 wherein X^2 is Br.

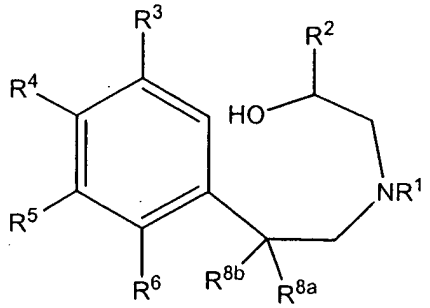
31. The process of claim 28 wherein X^2 is Cl.

32. The process of claim 28 wherein said reacting is carried out in the presence of a solvent comprising dimethylformamide or toluene.

33. The process of claim 28 wherein said elevated temperature is from about -40 to about 80 °C.

34. The process of claim 28 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

35. A process for preparing a compound of Formula X:



X

or salt thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

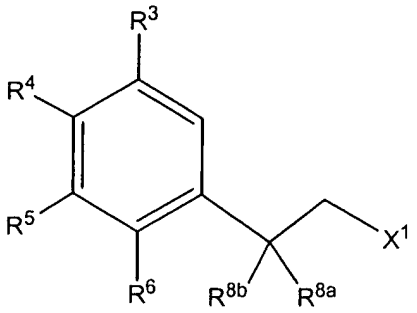
R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

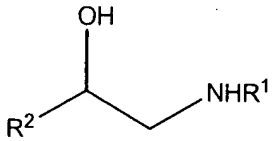
comprising reacting a compound of Formula XI:



XI

wherein X^1 is a leaving group,

with a compound of Formula:



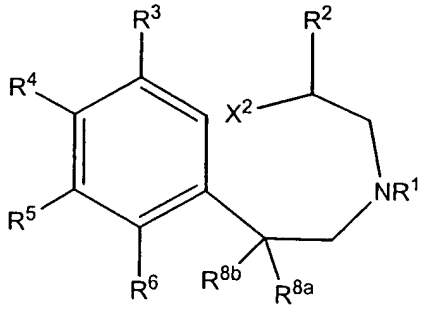
for a time and under conditions suitable for forming said compound of Formula X:

36. The process of claim 35 wherein X^1 is Br.

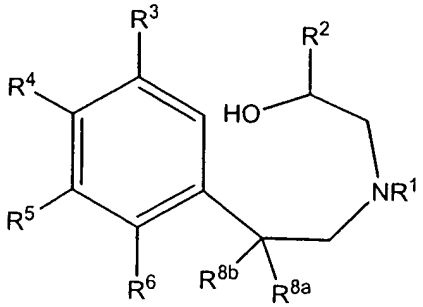
37. The process of claim 35 wherein said temperature is from about 80 to about 110 °C.

38. The process of claim 35 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

39. A compound of Formula IX or X:



IX



X

or salt form thereof,

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), or C_1-C_4 haloalkyl;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl;

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

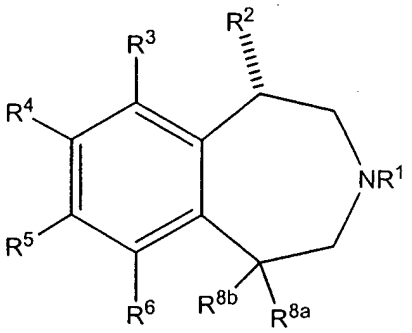
X^2 is halo or SO_2R"; and

R" is C_1-C_8 alkyl, aryl, or heteroaryl each optionally substituted by one or more halo, cyano, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy.

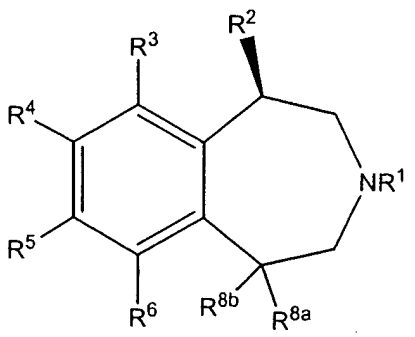
40. The compound of claim 39 wherein X^2 is Cl.

41. The compound of claim 39 or 40 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

42. A method of resolving a mixture of compounds of Formula Va and Vb:



Va



Vb

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), OH, C_1-C_4 haloalkyl, or CH_2OH;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring;

comprising:

contacting said mixture of compounds with a chiral resolving acid to form chiral resolving acid salts of said compounds, wherein said chiral resolving acid comprises substantially one stereoisomer; and

precipitating said chiral resolving acid salts of said compounds, wherein the resulting precipitate is enriched in the chiral resolving acid salt of one of said compounds of Formula Va or Vb.

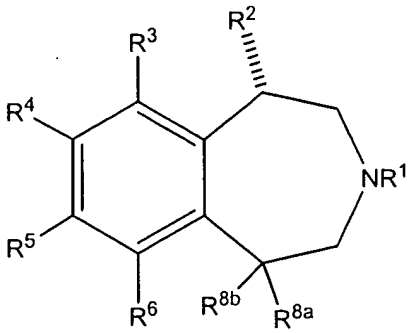
43. The method of claim 42 wherein said chiral resolving acid is tartaric acid.

44. The method of claim 42 wherein said chiral resolving acid is L-(+)-tartaric acid.

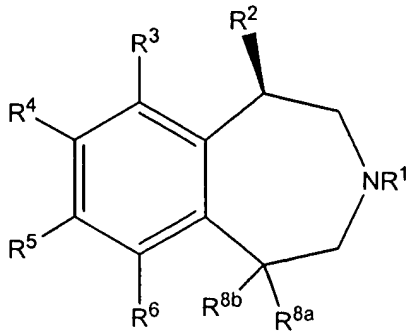
45. The method of claim 42 wherein said precipitate is enriched in the chiral resolving acid salt of said compound of Formula Vb.

46. The method of claim 42 or 44 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

47. A chiral resolving acid salt of a compound of Formula Va or Vb:



Va



Vb

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), OH, C_1-C_4 haloalkyl, or CH_2OH;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring.

48. The salt of claim 47 wherein said salt is a tartaric acid salt.

49. The salt of claim 47 wherein said tartaric acid is L-(+)-tartaric acid.

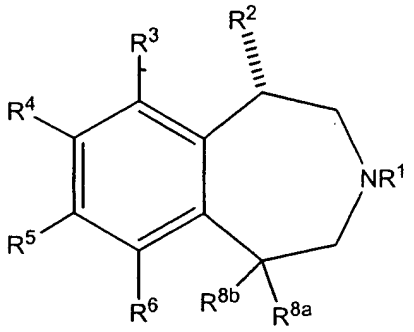
50. The salt of claim 47 having Formula Vb.

51. The salt of claim 47, 49, or 50 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

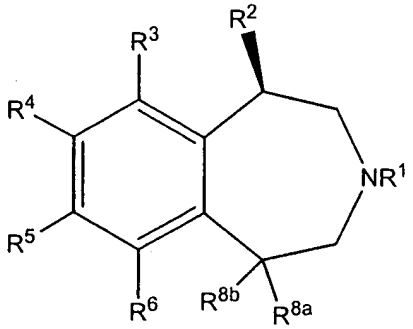
52. A composition comprising at least one chiral resolving acid salt of claim 47.

53. The composition of claim 52 wherein said composition comprises said tartaric acid salt form of a compound of Formula Va and said tartaric acid salt form of a compound of Formula Vb, wherein said composition is enriched in one of either of said tartaric acid salt form of a compound of Formula Va or said tartaric acid salt form of a compound of Formula Vb.

54. A hydrochloric acid salt of a compound of Formula Va or Vb:



Va



Vb

wherein:

R^1 is H or C_1-C_8 alkyl;

R^2 is C_1-C_8 alkyl, -CH_2-O-(C_1-C_8 alkyl), C(O)O-(C_1-C_8 alkyl), -C(O)NH-(C_1-C_8 alkyl), OH, C_1-C_4 haloalkyl, or CH_2OH;

R^3, R^4, R^5, and R^6 are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, hydroxy, OR^9, alkoxyalkyl, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, hydroxyalkyl, $NR^{10}R^{11}$, CN, NO_2, heterocycloalkyl, aryl, or heteroaryl, wherein said aryl and heteroaryl can be substituted with one or more substituents selected from C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, and alkoxy; or R^4 and R^5 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

R^{8a} and R^{8b} are each, independently, H, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, alkoxyalkyl, hydroxy, C(O)-alkyl, C(O)O-alkyl, C(O)NH-alkyl, or hydroxyalkyl, or R^{8a} and R^{8b} together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^9 is H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl; and

R^{10} and R^{11} are each, independently, H, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 haloalkyl, aralkyl, aryl, heteroaryl, heteroarylalkyl, or allyl, or R^{10} and R^{11} together with the N atom to which they are attached form a heterocyclic ring.

55. The salt of claim 54 having Formula Vb.

56. The salt of claim 54 or 55 wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

57. The salt of claim 54 having Formula Vb wherein R^1 is H, R^2 is Me, R^3 is H, R^4 is Cl, R^5 is H, R^6 is H, R^{8a} is H, and R^{8b} is H.

58. A composition comprising at least one hydrochloric acid salt of claim 54.

ABSTRACT

The present invention provides processes and intermediates for the preparation of 3-benzazepines and salts thereof which can be useful as serotonin (5-HT) receptor agonists for the treatment of, for example, central nervous system disorders such as obesity.